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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,060	02/17/2004	Spyridon Artavanis-Tsakonas	7326-131	8375

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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
BALLARD, KIMBERLY	
ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,060	ARTAVANIS-TSAKONAS ET AL.	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009 and 14 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,91-94,96-106,108-111 and 113-116* is/are pending in the application.

4a) Of the above claim(s) *101-106,108-111,113,114 and 116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,91-94 and 115* is/are rejected.

7)☒ Claim(s) *96-100* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kimberly Ballard, Art Unit 1649.

Status of Application, Amendments, and/or Claims

2. Claims 34 and 96 have been amended and claim 95 has been canceled as requested in the response filed November 14, 2008. Following the amendment, claims 34, 91-94, 96-106, 108-111 and 113-116 are pending in the current application. Claims 101-106, 108-111, 113, 114 and 116 have been withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species, there being no allowable generic or linking claim.

3. Accordingly, claims **34, 91-94, 96-100** and **115** are under examination in the current office action.

Inventorship

4. In view of the papers filed February 11, 2008, the inventorship in this nonprovisional application has been changed by the deletion of Richard Grand Fehon and Christine Marie Blaumueller.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Withdrawn Objections and Claim Rejections

5. The objection to the specification set forth at paragraph 10 of the previous office action (mailed 05/14/2008) is withdrawn in view of Applicant's amendments to the specification.

6. The rejection of claims 34 and 96 under 35 U.S.C. 102(e) as being anticipated by US Patent 5,211,657 to Yamada et al., as discussed at paragraphs 11-14 of the previous office action, is withdrawn in view of applicants' arguments particularly at p. 7. It is noted that this rejection as it pertains to claim 106 is moot on account of the fact that the claim had been (and still is) withdrawn from examination.

7. The rejection of claims 97-99 under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. (5,211,657) in view of Harlow and Lane (Cold Spring Harbor Laboratory, 1988), as discussed at paragraphs 15-18 of the previous office action, is withdrawn in view of Applicants' arguments. Note that this rejection as it pertains to claims 95 and 109-110 is rendered moot on account of the claims either having been cancelled or withdrawn from examination.

8. The rejection under 35 U.S.C. 112, first paragraph (scope of enablement), as discussed at paragraphs 19-28 of the previous office action, is withdrawn (in part) for claims 96-100 in view of Applicants' arguments and amendments to the claims. See section on 35 U.S.C. § 112, first paragraph, below for maintained portions of the rejection.

9. The rejection under 35 U.S.C. 112, first paragraph (written description), as discussed at paragraphs 29-32 of the previous office action, is withdrawn (in part) for claims 96-100 in view of Applicants' arguments and amendments to the claims. See section on 35 U.S.C. § 112, first paragraph, below for maintained portions of the rejection.

10. The rejection of claims 34, 91-94, 96-100 and 115 under 35 U.S.C., 112, first paragraph (new matter), as set forth at paragraphs 33-35 of the previous office action, is withdrawn in view of Applicants' amendments to the specification.

Maintained Claim Rejections

Claim Rejections - 35 USC § 112, first paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 34, 91-94 and 115 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of treating a disease or disorder in a human in which the disease or disorder is a malignancy characterized by increased Notch activity or increased expression of a human Notch protein or of a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said Notch activity or expression in an analogous non-malignant sample, comprising administering to a human in need of such treatment a therapeutically effective amount of a molecule which antagonizes the function of a human Notch protein (claim 34), wherein the molecule interferes with Notch intracellular signal transduction (claim 115). Hence, the claims are drawn to a therapeutic method of using a genus of molecules that antagonize the function of, or interfere with intracellular signal transduction of, human Notch protein.

13. In the response filed November 14, 2008, Applicants argue that contrary to the Examiner's statement of the previous Office action, the claimed invention is not directed to treating any disease. Applicants assert that the invention is directed to treating a disease or disorder which is a malignancy characterized by increased Notch activity or increased Notch expression. Further, Applicants argue that contrary to the Office's interpretation, the claimed invention is not directed to administering antibodies to Notch

derivatives, but to administering antibodies that antagonize the function of a human Notch protein, such as an antibody to said human Notch protein.

14. Applicants' arguments have been fully considered and are persuasive in part. With respect to the treatment of a disease, the Examiner concedes that the claimed method is directed to the treatment of those diseases and disorders which are malignancies characterized by increased Notch activity or expression. With respect to the argument regarding Notch antibodies, Applicants' arguments are persuasive and thus the rejection has been withdrawn with respect to instant claims 96-100 as indicated *supra*.

However, the breadth of claims 34, 91-94, and 115 still encompasses the use of a broad genus of antagonistic molecules for which inadequate guidance or support is provided in the present disclosure. For example, the specification teaches that "Antagonist Therapeutics" include but are not limited to Notch antisense nucleic acids, anti-Notch neutralizing antibodies, and competitive inhibitors of Notch protein-protein interactions (e.g., a protein comprising Notch ELR-11 and ELR-12 (EGF-like repeat) and derivatives thereof) (page 5, lines 1-8). At page 11, lines 11-22, therapeutic compounds of the invention are also disclosed to include: "Notch proteins and analogs and derivatives (including fragments) thereof; antibodies thereto; nucleic acids encoding the Notch proteins, analogs, or derivatives; Notch antisense nucleic acids; as well as toporythmic proteins and derivatives and analogs thereof which bind to or otherwise interact with Notch proteins, and their encoding nucleic acids and antibodies. Also included are proteins and derivatives and analogs thereof which are capable of

inhibiting the interactions of a Notch protein with another toporythmic protein (e.g., Delta, Serrate)." Thus, it can be seen that the claimed method encompasses the use of a vast genus of nucleic acid and amino acid molecules with widely varying sequences and structures of both defined and as-yet-undefined molecules. The claims encompass the use of *any* molecule that can antagonize or interfere with Notch function, which would be inclusive not only of molecules that directly inhibit Notch itself, but also of molecules which indirectly antagonize Notch function by blocking or inhibiting Notch ligands, Notch downstream signaling molecules, or other toporythmic proteins such as Delta or Serrate. Therefore, the recitation of "a molecule which antagonizes the function of a human Notch protein" does not meet the written description provision of 35 U.S.C. 112, first paragraph, because there is insufficient guidance and direction of the claimed molecule as broadly encompassed by the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Applicants are directed to the recently-published guidelines on interpretation of the written description requirement, available on the internet at: http://www.uspto.gov/web/menu/written.pdf . In this case, the only factor present in the claim is a recitation of desired function. The brief description in the specification describing antibodies to human Notch homologs hN and TAN-1, or Notch antisense nucleic acid molecules, does not comprise a representative

number of species for the broad genus of antagonist molecules capable of antagonizing the function of a human Notch protein or interfering with Notch intracellular signal transduction, such as for treatment of malignancies. For example, in a recent review by Kopan et al. (*Cell*, April 17 2009; 137:216-233), it is noted that dozens of molecules are involved in Notch signaling (see in particular Figures 1 and 2 and Table 1). Not all of these were known at the time the instant invention was filed, indicating that the full aspects of Notch signaling are complex and far-reaching. As claimed, any antagonist of any of the molecules involved in Notch signaling (such as those molecules taught by Kopan et al. which were even defined at the time of filing) could potentially be used in the claimed method.

However, other than for antagonists which directly and specifically bind to human Notch, the specification does not identify the structures or structure/function correlations of agents capable of indirectly antagonizing Notch function or intracellular signaling, nor is there identification of any particular portion of the structures of these other molecules that must be conserved. Distinguishing structural characteristics that could help to identify members of the claimed genus of antibodies, polypeptides, or nucleic acids from others in their respective classes are lacking from the instant specification. The skilled artisan would thus not have recognized that Applicants were in possession of the vast repertoire of antagonist molecules encompassed by the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus nor guidance as to which of myriad of molecules that are encompassed by the claimed

Notch antagonists would be effective in the treatment of malignancy characterized by increased Notch activity and/or expression in a subject.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed Notch antagonists, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identification and isolation of such antagonists. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 (BPAI 1993). In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the use of antibodies that specifically bind to human Notch protein, antibodies containing the idiotype thereof, and Notch antisense nucleic acid, but

not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

15. Claims 34, 91-94 and 115 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a disease or disorder in a human, in which the disease or disorder is a malignancy characterized by increased Notch activity or increased expression of a human Notch protein or of a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said Notch activity or expression in an analogous non-malignant sample, comprising administering to the human in need of such treatment a therapeutically effective amount of a molecule which antagonizes the function of a human Notch protein, wherein the molecule is a neutralizing anti-Notch antibody or portion of said antibody containing the idiotype thereof, does not reasonably provide enablement for a method of treating such malignancies by administering any molecule which antagonizes the function of a human Notch protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

16. In the response filed November 14, 2008, Applicants argue that the claims, as amended, are not directed to treating any disease, nor are they directed to administering any molecule that antagonizes or binds to a Notch derivative. Rather, the

amended claims recite a method of treating a disease or disorder that is a malignancy that is characterized by increased Notch activity or increased expression of a human Notch protein or of a Notch derivative that is recognized by an antibody to a human Notch protein. Applicants also assert that the claims, as amended, specify administering a therapeutically effective amount of a molecule which antagonizes the function of a human Notch protein, not any Notch derivative to treat any disease. Applicants note that the specification demonstrates that an antibody to Notch can antagonize Notch function, and that post-filing art (Li et al., *J Biol. Chem*. 2008 Mar; 283(12):8046-8054; of record) "clearly shows that anti-Notch antibodies are capable of acting as antagonists of Notch function." Further, at pp. 10-11 Applicants cite numerous references (all of record), and assert that such references show that activated Notch function is associated with malignancy as well as suggesting that antagonizing Notch can be therapeutically useful in the treatment of such malignancies. Applicants therefore conclude that the foregoing evidence is sufficient to convince one skilled in the art that antagonists of Notch function (e.g., antibodies to human Notch) can be used to treat malignancy.

17. Applicants' arguments have been fully considered and are persuasive in part. Specifically, with respect to claims 96-100, which are drawn to antagonist molecules that are anti-Notch antibodies, this rejection has been withdrawn as indicated supra. With respect to arguments regarding the treatment of "any" disease, Applicants' amendments to the claims and arguments are also similarly convincing. However, the issue remains that claims 34, 91-94 and 115, as broadly interpreted, still broadly

encompass the therapeutic use of any molecule which antagonizes the function of a human Notch protein. The scope of enablement has been adjusted accordingly in maintenance of this rejection and in view of Applicants' persuasive arguments and amendments to the claims.

The broadest reasonable interpretation of the claims includes the therapeutic use of a extremely large genus of therapeutic molecules which antagonizes the function of a human Notch protein and, as discussed above, Applicants have not described all ot the common features of the genus such that the skilled artisan would recognize that Applicants were in possession of such molecules.

Neither the evidence provided in the specification nor that of the post-filing art references is commensurate in scope with the broadly claimed genus of antagonist molecules. Such examples are limited to antagonist anti-Notch antibodies, Notch antisense, or γ-secretase inhibitors for the proposed treatment of malignancies. Because there are dozens of molecules involved in Notch signaling (not of which were even known at the time of filing), antagonists to any of these molecules would meet the limitation of "a molecule which antagonizes the function of Notch" as disclosed in the instant specification. As noted in the previous office action, the state of the art to which the instant invention pertains is highly complex and unpredictable with respect to treatment of cancer and malignancies. Undue experimentation would therefore be required of the skilled artisan to determine which of the multitude of molecules in the Notch signaling pathway could be antagonized in order to obtain predictable therapeutic results.

The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to practice the claimed invention with the plurality of Notch antagonist molecules encompassed by the claims, the absence of working examples directed to same, the state of the art which establishes the unpredictability of such treatment, and the breadth of the claims, undue experimentation would be required of the skilled artisan to practice the invention commensurate in scope with the claimed method.

Conclusion

18. Claims 34, 91-94 and 115 are rejected.

19. Claims 96-100 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. It is noted that new references were relied upon to support the previously made and maintained rejections under 35 U.S.C. § 112, first paragraph. Applicants are advised that any new arguments or evidence submitted to address these new references will be entered and given full consideration if submitted with an after final amendment.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard
Art Unit 1649

/Elizabeth C. Kemmerer/
Elizabeth C. Kemmerer, Ph.D.
Primary Examiner, Art Unit 1646